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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,739	08/25/2003	Manuel Guzman Pastor	A34700 PCT USA-I	2301

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DLNYDOCKET@BAKERBOTTS.COM

Office Action Summary	Application No.	Applicant(s)	
	10/647,739	GUZMAN PASTOR ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response, filed 9/30/2008, are acknowledged and entered. Claim 16 are pending and under examination.

There is only one remaining issue in the present case: whether it would have been obvious to one of ordinary skill in the art at the time the invention was made to have administered Δ9-tetrahydrocanabinol or Δ8-tetrahydrocannibinol to a mammal having a glioblastoma in view of the cited prior art that teaches that Δ9-tetrahydrocanabinol induces apoptosis of C6 gliomas cells in vitro and that teaches that C6 glioma cells are an art-recognized model of glioblastomas. The Examiner finds that such administration would have been prima facie obvious and that the skilled artisan would have been imbued with at least a *reasonable expectation* of success. Applicant disagrees.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 16 is again rejected under 35 U.S.C. § 103(a) as being unpatentable over **Sanchez *et al.*** (FEBS Letters, 1998, vol. 436, pages 6-10) in view of **Uesugi *et al.*** (Acta Neuropathol., 1998, vol. 96, pages 351-356).

The instant claim recites a method of treating glioblastomas in a mammal comprising administering Δ^9-tetrahydrocannabinol (Δ^9-THC) or Δ^8-tetrahydrocannabinal (Δ^8-THC).

Sanchez *et al.* disclose that Δ^9-THC induces apoptosis in C6 glioma cells (Abstract; Figures). The authors suggest that the challenge of C6.9 cells to cannabinoids may be a useful model to study the molecular mechanisms involved in apoptosis in cells of glial origin (page 9, right column).

C6 glioma cells are art-recognized as a model of glioblastomas. For example, Uesugi *et al.* discloses the use of a rat glioma cell line (C6) as a rat glioma model (Abstract; page 351). Apoptosis of glioma cells is induced by the administration of several agents, including anti-tumor drugs (*id.*). C6 glioma cells are traditionally used as a model of glioblastoma multiforme when implanted in rat brains (page 354).

In view of the teachings of the cited references, the instantly claimed method of treating glioblastomas by administering Δ^9-THC or Δ^8-THC would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Sanchez *et al.* demonstrate that Δ^9-THC induces apoptosis in C6 glioma cells. As such, the skilled artisan would have been motivated to use Δ^9-THC to treat glioblastomas given the fact that C6 gliomas cells were recognized in the art as a model of glioblastoma growth, invasion and metastases. Further, the skilled artisan would have been imbued with at least a reasonable expectation that a compound that induces apoptosis of C6 glioma cells *in vitro* would also be effective in treating a glioblastoma *in vivo*.

Applicants' arguments and secondary considerations have been thoroughly considered but they are not found persuasive. Applicants submit that the Examiner has not met his burden of establishing obviousness under 35 U.S.C. 103(a). In support of this argument, Applicant cites the Supreme Court decision in *KSR International v. Teleflex, Inc.* Applicants note that a standard of "reasonable" predictiveness is an inappropriate consideration in an of itself in determining obviousness and that in view of pertinent art, Applicants submit that there is absent a "reasonable expectation of success".

Applicants argue that one skilled in the art would not consider the in vitro treatment method of Sanchez for glioblastomas to be reasonably applied in vivo. Applicants submit that

these particular references teach in vitro results that are "simply that and nothing more" and are in no way indicative of in vivo treatment or success. In response, the Examiner respectfully submits that in vitro efficacy of a chemical compound are well established in the art as a first step in identifying new agents to treat disease. The next logical, obvious step is to test chemical compounds found effective in vitro in established in vivo models of the same disease. That is all Applicants have done in the present case.

Applicants argue that the Examiner must resolve the level of ordinary skill in the pertinent art. In this regard, Applicants assert that at the time of filing of the application, it was "impossible" to simply extrapolate in vitro teachings to in vivo treatment with "any degree of expectation of success for glioblastomas". Applicants assert that the Examiner has "simply ignored" the numerous submissions by the Applicants that demonstrate the numerous failures of scientists in the art to use the treatment in vivo based on in vitro studies. This is, however, simply not true. The Examiner has carefully considered all of the pertinent art, including the art cited by the Examiner demonstrating that compounds found to be effective in vitro for treating glioblastomas were also found to be effective in vivo. While it is certainly true that there are also many examples wherein in vitro effective compounds were not effective in vivo, there are also many examples of compounds that are effective both in vitro and in vivo for the treatment of glioblastoma. Applicants are reminded that a *guarantee* of success is **not** the standard for establishing obviousness. All the statute requires is a *reasonable expectation* of success. Based on the totality of the pertinent art, the Examiner respectfully submits that the skilled artisan would have been imbued with at least a reasonable expectation that Δ^9-THC would be effective in vivo based upon its proven efficacy in vitro.

Applicants refer to Castro et al. and assert that in Table 2, Castro discloses a listing of chemotherapeutic agents "normally used to treat tumors, however, **all** such agents are ineffective to treat glioblastomas in vivo". The title of Table 2 in Castro is "Chemotherapeutic agents **used for the treatment of brain tumors**". Brain tumor types disclosed to be treated by at least some of the listed chemotherapeutic agents include "malignant glioma". Castro states that the use of chemotherapy is now **well established** in the treatment of brain tumors (page 75, left column). As such, Applicants' characterization of the teachings of Table 2 of Castro are misleading.

Applicants reiterate that there is no reasonable expectation of success and that the Examiner must take into account secondary consideration. These issues have been discussed *supra* and the Examiner refers Applicants to his response supra. Applicants further submit that the fact that they have demonstrated that Δ^9-THC is effective to treat glioblastomas in vivo is an unexpected result. The Examiner does not find this persuasive for the reasons discussed supra. The skilled artisan would have been imbued with at least a reasonable expectation that Δ^9-THC would be effective in vivo based upon its proven efficacy in vitro. Applicants are again reminded that a *guarantee* of success is **not** the standard for establishing obviousness. All the statute requires is a *reasonable expectation* of success.

Accordingly, the claim is deemed properly rejected under 35 U.S.C. § 103 as being *prima facie* obvious over the cited references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614